Amendments to the Abstract:

Please replace the original Abstract with the following redlined Abstract:

Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. The compositions comprise ~~one or more of a WT1 polynucleotide,~~ a WT1 polypeptide comprising an immunogenic portion of WT1, wherein said WT1 polypeptide comprises the polypeptide of SEQ ID NO:144., ~~an antigen-presenting cell presenting a WT1 polypeptide, an antibody that specifically binds to a WT1 polypeptide; or a T cell that specifically reacts with a WT1 polypeptide~~. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A polypeptide ~~comprising~~ consisting of an immunogenic portion of a native WT1~~, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with WT1-specific antisera and/or T-cell lines or clones is not substantially diminished~~, wherein the polypeptide ~~comprises~~ consists of the polypeptide set forth in SEQ ID NO:144.

2-5. (Canceled)

6. (Currently Amended) A polypeptide according to claim 1, wherein the polypeptide ~~comprises~~ consists of 4-9 consecutive amino acids of SEQ ID NO:144.

7. (Currently Amended) A polypeptide according to claim 1, wherein the polypeptide ~~comprises~~ consists of 8-9 consecutive amino acids of SEQ ID NO:144.

8-45. (Canceled)

46. (Withdrawn) The polypeptide of claim 1, wherein said immunogenic portion differs from SEQ ID NO:144 at between 1 and 3 amino acid positions, such that the ability of the polypeptide to react with WT1-specific antisera and/or T-cell lines or clones is enhanced relative to a native WT1.

47. (Currently Amended) A composition comprising ~~any one of~~ the polypeptides of claim 1 ~~or claim 46~~ in combination with a pharmaceutically acceptable carrier or excipient.

48. (Currently Amended) An immunogenic composition comprising ~~any one of~~ the polypeptides of claim 1 ~~or claim 46~~ in combination with a non-specific immune response enhancer.

49. (Previously Presented) The immunogenic composition according to claim 48 wherein the non-specific immune response enhancer preferentially enhances a T cell response in a patient.

50. (Previously Presented) The composition according to claim 48, wherein the immune response enhancer is selected from the group consisting of Montanide ISA50, Seppic Montanide ISA 720, a cytokine, a microsphere, dimethyl dioctadecyl ammoniumbromide (DDA) based adjuvants, AS-1, AS-2, Ribi Adjuvant system based adjuvant, QS21, saponin based adjuvants, Syntex adjuvant in its microfluidized form, MV, ddMV, immune stimulating complex (iscom) based adjuvants, and inactivated toxins.

51. (Previously Presented) The composition of claim 50, wherein said cytokine comprises GM-CSF.

52.-54. (Canceled)

55. (Withdrawn) The polypeptide of claim 52, wherein said immunogenic portion differs from WT1 at between 1 and 3 amino acid positions, such that the ability of the polypeptide to react with WT1-specific antisera and/or T-cell lines or clones is enhanced relative to a native WT1.

56. (Canceled)

57. (Currently Amended) An immunogenic composition comprising ~~any one~~ an isolated polypeptide comprising a WT1 polypeptide, wherein the WT1 polypeptide consists of

no more than amino acids 1-249 of WT1 and comprises the amino acid sequence set forth in SEQ ID NO:144~~of the polypeptides of claim 52 or claim 55~~ in combination with a non-specific immune response enhancer, wherein the non-specific immune response enhancer preferentially enhances a T cell response in a patient.

58. (Canceled)

59. (Previously Presented) The composition according to claim 57, wherein the immune response enhancer is selected from the group consisting of Montanide ISA50, Seppic Montanide ISA 720, a cytokine, a microsphere, dimethyl dioctadecyl ammoniumbromide (DDA) based adjuvants, AS-1, AS-2, Ribi Adjuvant system based adjuvant, QS21, saponin based adjuvants, Syntex adjuvant in its microfluidized form, MV, ddMV, immune stimulating complex (iscom) based adjuvants, and inactivated toxins.

60. (Previously Presented) The composition of claim 59, wherein said cytokine comprises GM-CSF.

61. (New) An isolated polypeptide comprising a WT1 polypeptide, wherein the WT1 polypeptide comprises amino acids 1-249 of WT1 and wherein said WT1 polypeptide does not comprise full-length WT1.

62. (New) An immunogenic composition comprising the isolated polypeptide of claim 61 in combination with a non-specific immune response enhancer, wherein the non-specific immune response enhancer preferentially enhances a T cell response in a patient.

REMARKS

Reconsideration of the above-identified application is respectfully requested. Claims 1, 6, 7, 46-60 are pending in this case. Applicants note that the Examiner has withdrawn claims 5, 8, 9-46 and 55. With the above amendment, claims 52-54, 56, and 58 have been canceled without prejudice and new claims 61 and 62 have been added. Accordingly, claims 1, 6, 7, 47-51, 57, and 59-62 are under consideration. Claims 1, 6, 7, 47, 48, and 57 have been amended for purposes of clarity and to advance prosecution of this application. It is urged that support for the above amendments can be found throughout the specification as originally filed and that none of the amendments constitutes new matter. In particular, support for full length WT1 can be found throughout the specification, for example, at page 8, lines 9-10; Figure 1; and SEQ ID NO:319. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter modified and/or removed in a related divisional, continuation and/or continuation-in-part application.

Claims Rejected Under 35 U.S.C. § 112, first paragraph

Claims 1, 47-52, and 56-60 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Action contends that the written description provided in the specification is not commensurate with the scope of the claimed "variants".

Applicants respectfully traverse this rejection and submit that as described in Applicants' specification, SEQ ID NO:144 represents a WT1 peptide with motifs appropriate for binding to MHC class I, and was identified using BIMAS HLA peptide binding prediction analyses (*e.g.*, see Tables V, XIII, XVI, XVII, XXIV, XXVI, XXVII, XXX, XXXII, XXXIII, XXXIV, XXXV, XXXVI, XXXVII and Table XLVIII) and was further shown to be a naturally processed cytotoxic T cell epitope using *in vitro* T cell assays (see *e.g.*, Example 5, at pages 113-116). Immunization with p117-139 peptide which comprises the peptide of SEQ ID NO:144,

was demonstrated by Applicants to elicit a proliferative T cell responses *in vivo* (*e.g.*, Example 3, at page 58, lines 18-26; also Figures 6A-6C). Moreover, the WT1-specific T cells stimulated *in vivo* were demonstrated, using a chromium release assay, to be capable of killing WT1 positive tumor cells, whereas no killing of WT1 negative tumor cells was observed (*e.g.*, and Example 5, at pages 113-116). Thus, Applicants have identified T cells specific for SEQ ID NO:144 that are capable of recognizing and lysing tumor cells expressing WT1.

Importantly, these WT1-specific T-cells identified by Applicants can be routinely isolated and used in the identification of the immunogenic variants of SEQ ID NO:144. For example, a series of variants of SEQ ID NO:144, having up to 3 amino acid substitutions, can be synthesized and compared with SEQ ID NO:144 in their ability to stimulate proliferation of the WT1-specific T-cells. As disclosed by Applicants, at page 17, lines 10-15:

> (T)he ability of a variant to react with antigen-specific antisera and/or T-cell lines or clones may be enhanced or unchanged, relative to the native polypeptide, or may be diminished by less than 50%, and preferably less than 20%, relative to the native polypeptide. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antisera and/or T-cells as described herein.

Applicants submit that the skilled artisan would readily understand, in light of Applicants' disclosure, the single identifying characteristic common to the claimed variants, *i.e.*, their ability to stimulate T cells specific for SEQ ID NO:144, and would further appreciate the routine nature of the techniques used in their identification. Thus, in view of Applicants specification, and the routine and art recognized approaches for the identification and evaluation of variants that are reactive with antigen-specific T-cells, the person of ordinary skill in the art would recognize that Applicants were indeed in possession of the presently claimed invention as of the filing date of the captioned application.

Notwithstanding the foregoing, and solely to advance prosecution, Applicants have amended claim 1 and canceled claim 52 to remove recitation of variants. Applicants have made these amendments without prejudice or acquiescence and reserve the right to prosecute any subject matter modified and/or removed in a related divisional, continuation and/or continuation-

in-part application. Accordingly, Applicants submit that the rejection has been obviated and respectfully request its withdrawal.

Claims Rejected Under 35 U.S.C. § 112, first paragraph

Claims 1, 6, 7, 47-54, and 56-60 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Action contends that the specification does not provide evidence (using actual assays) that demonstrate that the claimed peptides are actually immunogenic with regard to stimulation of T cells. The Action therefore concludes that undue experimentation would be required of one skilled in the art to practice the instant invention.

Applicants respectfully traverse this rejection and submit that the specification as filed does indeed provide evidence that the claimed peptide is actually immunogenic. In particular, Applicants direct the Examiner to Example 5, at pages 113-116 where the specification describes the *in vitro* experiment showing that the peptide of SEQ ID NO:144 is a naturally processed cytotoxic T cell (CTL) epitope:

> Several segments with putative CTL motifs are contained within p117-139 [SEQ ID NO:2]. To determine the precise sequence of the CTL epitope all potential 9-mer peptides within p117-139 were synthesized (Table XLVIII). Two of these peptides (p126-134 and p130-138 **[SEQ ID NO:144]**) were shown to bind to H-2^b class I molecules (Table XLVIII). CTL generated by immunization with p117-139 lysed targets incubated with p126-134 and p130-138, but not the other 9-mer peptides within p117-139 (Figure 13A).
> The p117-139 specific CTL line was restimulated with either p126-134 or p130-138. Following restimulation with p126-134 or p130-138, both T cell lines demonstrated peptide specific lysis, but **only p130-138 [SEQ ID NO:144] specific CTL showed lysis of a WT1 positive tumor cell line (Figures 13B and 13C). Thus, p130-138 appears to be the naturally processed epitope.** (emphasis added)

Therefore, Applicants submit that the specification as filed enables the skilled artisan to make and/or use the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claims Rejected Under 35 U.S.C. § 102(b)

Claims 1, 6, 7, 47, 52, and 56 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Herlyn *et al.* (WO 95/29995). In particular, the Action alleges that Herlyn *et al.* teaches a peptide comprising SEQ ID NO:144 wherein said peptide is immunogenic (*e.g.*, it induces antibodies).

While not acquiescing to the Examiner's rejection, the presently amended claims are now directed to a polypeptide consisting of an immunogenic portion of a native WT1, wherein the immunogenic portion consists of SEQ ID NO:144 and compositions comprising said polypeptide. Applicants submit that the presently claimed invention is indeed novel over Herlyn *et al.*, on the basis that this reference fails to teach an immunogenic WT1 peptide consisting of SEQ ID NO:144, much less that the peptide is effective for eliciting T helper and/or CTL responses. Further, solely to advance prosecution, and without acquiescence to the rejection, Applicants have canceled claims 52 and 56. Accordingly, Applicants submit that this ground for rejection has thus been obviated and respectfully request its withdrawal.

Claims Rejected Under 35 U.S.C. §§ 102(e) or 102(a)

Claims 1, 6, 7, 47, 48, 52, 56, 57 stand rejected under 35 U.S.C. § 102(e) or 102(a) as being anticipated by Call *et al.* (U.S. Patent 5,726,288). Call *et al.* allegedly teach an immunogenic peptide comprising SEQ ID NO:144 wherein said peptide is in a pharmaceutically acceptable excipient and wherein variants of the peptide are used with a non-specific immune response enhancer.

Applicants note that solely to advance prosecution, claims 52 and 56 have been canceled without prejudice and without acquiescence to the rejections. Applicants submit that the pending claims 1, 6, 7, 47, and 48, have been amended without acquiescence to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:144. Call *et al.* describe the use

of WT1 and two different WT1 peptides to generate poly and monoclonal antibodies in mice. Neither of the peptides used by Call *et al.*, however, consist of the sequence set forth in SEQ ID NO:144, nor does Call *et al.* teach or suggest that a WT1 peptide consisting of SEQ ID NO:144 would be capable of effectively eliciting an immune response. With regard to amended claim 57 and newly added claims 61 and 62, Applicants submit that nowhere does Call *et al.* teach or suggest a WT1 polypeptide consisting of no more than amino acids 1-249 of WT1 and wherein said polypeptide comprises the amino acid sequence of SEQ ID NO:144, or a WT1 polypeptide comprising 1-249 wherein said WT1 polypeptide does not comprise full length WT1, let alone that such WT1 polypeptides would be capable of effectively eliciting a T cell response. Thus, Applicants respectfully submit that Call *et al.* does not anticipate the presently claimed subject matter. Applicants submit that this ground for rejection has been obviated and respectfully request reconsideration and withdrawal of the rejection.

Claims Rejected Under 35 U.S.C. § 103(a)

Claims 1, 6, 7, 47-52, and 56-60 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Herlyn *et al.* (WO 95/29995) or Call *et al.* (U.S. Patent 5,726,288) in view of Jager *et al.* (U.S. Patent 6,096,313). Herlyn *et al.* and Call *et al.* are discussed above. Jager *et al.* describes the use of GM-CSF as an adjuvant.

Applicants again note that claims 52 and 56 have been canceled without prejudice or acquiescence. Applicants further reiterate that pending claim 1 and claims 6, 7, and 47-51 dependent therefrom have been amended without acquiescence to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:144. Applicants' arguments to the Examiner's position under 35 U.S.C. sections 102(e) and 102(a) regarding Herlyn *et al.* and Call *et al.* are equally applicable in the context of this rejection under 35 U.S.C. 103(a). As set forth above, Herlyn *et al.* and Call *et al.* fail to teach the specific WT1 immunogenic portions presently claimed by Applicants. Likewise, Jager *et al.* fails to teach the specific WT1 immunogenic portions presently claimed. In view of this, Applicants respectfully submit that the cited references, taken either alone or in combination, cannot reasonably render obvious the presently claimed WT1 immunogenic portion consisting of SEQ ID NO:144, when the cited references

offer no teaching or suggestion as to the existence and/or the identity of the now claimed immunogenic portion.

With regard to amended claims 57 and 59-60, Applicants submit that Herlyn *et al.* teach the use of a fragment of WT1 consisting of amino acids 1-181 as a tool to generate antibodies in mice. Nowhere does Herlyn *et al.* teach or even suggest that a WT1 polypeptide consisting of no more than amino acids 1-249 of WT1 wherein said polypeptide comprises the amino acid sequence of SEQ ID NO:144, or any portion of WT1 for that matter, would be capable of effectively eliciting a T cell response. Moreover, nowhere does Herlyn *et al.* even suggest that it would be desirable to elicit a WT1-specific T cell response. As noted above, Jager *et al.* simply describes the use of GM-CSF as an adjuvant. Nowhere does this reference teach or suggest WT1 or any peptides or immunogenic fragments thereof. With regard to newly added claims 61 and 62, nowhere do the cited references teach or suggest a WT1 polypeptide comprising 1-249 wherein said WT1 polypeptide does not comprise full length WT1, or that such a WT1 polypeptide would be capable of effectively eliciting a T cell response.

Even assuming *arguendo* that the cited references show elements of Applicants' invention, there is no motivation for a skilled artisan to combine the cited references in order to arrive at Applicants' claimed invention. As the Federal Circuit has recently reiterated, "virtually all inventions are combinations of old elements." Further, the Court noted that although an Examiner may often find every element of a claimed invention in the prior art, such a finding is insufficient to support a *prima facie* case of obviousness. To properly support a *prima facie* case of obviousness, the Examiner must show a motivation to combine the references. To this end, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet,* 47 USPQ2d 1453, 1458 (Fed. Cir. 1998) Further, when an Examiner relies on the skill in the art, the Examiner must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *Id.* As noted by the Federal Circuit, if merely "a rote invocation [of the skill in the art] could suffice to supply motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a

patentable technical advance." *Id.* Applicants submit that the skilled artisan would have had no motivation to combine the cited references to arrive at Applicants' invention.

Without motivation to combine the prior art references, a skilled artisan would select and combine elements from the prior art only by examining the problem in hindsight. The Federal Circuit has firmly rejected such hindsight reconstruction used to "pick and choose among isolated disclosures in the prior art" to arrive at Applicants' invention. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). To this end, Applicants submit that no specific reasoning has been given for a skilled artisan to combine the cited prior art references. Accordingly, Applicants submit that the cited prior art references support only a mere hindsight reconstruction of Applicants' invention.

In light of the above remarks, Applicants respectfully submit that the claimed invention is not obvious in view of the cited references and respectfully request reconsideration and withdrawal of the rejection.

Applicants respectfully submit that all the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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